382.1031CON

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Application of:	Yoshihiro YOSHIHARA
	Serial No.:	10/620,148
	Filed:	July 14, 2003
	For:	**MODEL ANIMALS FOR VISUALIZATION OF NEURAL PATHWAYS**
	Examiner:	Joanne Hama
	Art Unit:	1632

Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

DECLARATION OF HIROSHI SUZUKI UNDER 37 C.F.R. § 1.132

S i r:

I, Hiroshi Suzuki, hereby declare that:

1. I received a Bachelors of Science degree in Agriculture from the School of Veterinary Medicine and Animal Science of Kitasato University in Sagamihara, Japan in 1983. I also received a Masters of Science degree in Agriculture from the Department of Animal Breeding and Reproduction of the Institute of Veterinary Medicine and Animal Science of Kitasato University in Sagamihara, Japan in 1985, and my thesis was entitled "Studies on the development of mouse embryos derived from fertilization in vitro." I further received a Ph.D. in Veterinary Medicine from the Department of Reproductive and Developmental Biology, Institute of Medical Science, of the University of Tokyo in Tokyo, Japan in 1995, and my thesis was entitled "Studies on the development of zona-free mouse embryos."

2. From 2001 to the present, I have been a Professor at Research Unit for Functional Genomics, National Research Center for Protozoan Diseases, in Obihiro University of Agriculture and Veterinary Medicine in Hokkaido, Japan. From 2002 to the present, I have been

a guest Professor at the Department of Developmental and Medical Technology, Graduate School of Medicine, of the University of Tokyo in Tokyo, Japan. A copy of my curriculum vitae is attached hereto as Exhibit 1.

3. I submit this declaration in support of a Response to the Office Action dated September 9, 2004 from the U.S. Patent and Trademark Office in connection with the above-identified application.

4. I understand that, in the Office Action dated September 9, 2004 with respect to this patent application, the Examiner rejected claims 1-5 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable a person skilled in the art to make and use the invention as claimed. With regard to claims 1-3, the Examiner contended that the specification, while being enabling for a transgenic mouse that expresses wheat germ agglutinin (WGA) under the control of the L7 or OMP promoter, does not reasonably provide enablement, without undue experimentation, for any other "transgenic animal" expressing a trans-synaptic protein, for any other trans-synaptic tracer protein, for any other promoter to drive expression in neurons or for any neural cells, other than ones that express trans-synaptic protein, under the control of the L7 or OMP promoter, since the field of transgenic mammals, including the pronuclear injection method of generating transgenic animals, was unpredictable at the time of the instant application in that results obtained with one species would not have been predictive of results that would be obtained for another species.

5. I submit this declaration in order to demonstrate that the production of the model animals, the method of screening, and the production of transgenic animals other than mice can be carried out undue experimentation based on the disclosure of the specification.

6. Contrary to the Examiner's contention that generation of transgenic animals using pronuclear microinjection is unreliable, transgenic mammals can be produced with high probability, and there are commercial suppliers for the production of transgenic rodents such as rats and mice (see, for example, Charles River Laboratories (www.criver.com) and Xenogen Biosciences Transgenic Technologies (www.xenogenbiosciences.com/index.html)). The

development of pronuclear microinjection technology in mammals other than rodents was reviewed by Robert J. Wall in *Cloning and Stem Cells*, Vol. 3, pp. 209-20 (2001).

7. With regard to the Examiner's reliance upon teachings by Mullins and Mullins (1996, J.Clin.Invest, 97: 1557-60) to supported the allegation that the generation of transgenic non-murine animals using pronuclear microinjection is unreliable, I point out that the limitations cited by Mullins and Mullins regarding the application of pronuclear microinjection to non-murine animals are caused mainly by economics (see page 1557, second column, first full paragraph, lines 1-5), not by technical reasons that exist in the construction of non-murine transgenic animals alone. Other effects, such as random integration in the host chromosome and position effect in the case of pronuclear microinjection, are commonly observed in the construction of transgenic animals, including mice. Instead, the difference between murine and non-murine animals in the construction of transgenic animal is an efficiency of transgene integration and yield of transgenic offspring.

8. The same authors, Mullins and Mullins, also published a review summarizing the result of transgenic animals other than mouse constructed at that time (see, Mullins and Mullins, *Hypertension*, Vol. 22, pp. 630-33 (1993)). Mullins and Mullins reported that the frequency of integration onto chromosome in the construction of transgenic rabbit is slightly lower (12.8%) than that in mouse (27%) (see page 631, second column, the second full paragraph, line 11-18), referring to the pioneer study by Hammer et al. (*Nature*, Vol. 315, pp. 680-83 (1985)).

9. The reproducible result for obtaining transgenic rabbits can be established with the common method of pronuclear microinjection even if its efficiency is slightly lower (12.8%) than the efficiency of transgenic mouse (27%) as seen in this review. Mullins and Mullins reported actual examples for generation of transgenic rats, rabbits, sheep, goats, pigs and cows in the same review (see the corresponding paragraph). Thus, the establishment of transgenic animals other than mouse has been realized at appropriately reproducible frequency. The lower frequency (efficiency or yield) in the production of the transgenic animals should not constitute a reason for rejection, and pronuclear injection technique is developed in mice with the highest

level mostly due to its the ease of operation and economy of using mice, as opposed to other animals, for this purpose.

10. Accordingly, I believe that claim 1-3 as amended are fully enabled by the specification as of the date when the invention was made such that it would not require undue experimentation to produce the model animals, the method of screening, and transgenic animals other than mice based on the disclosure of the specification.

I hereby declare that I understand the English language and that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued therefrom.

Hiroshi Suzuki, Ph.D.

Dated: Hokkaido, Japan
January 21, 2005

CURRICULUM VITAE

Name, Family name:	Suzuki
Forenames:	Hiroshi
Sex:	Male
Date of birth:	6 October 1958
Place of birth:	Sapporo, Japan
Marital status:	Married
Nationality:	Japanese
Present address:	National Research Center for Protozoan Diseases, Obihiro University of Agriculture and Veterinary Medicine, Obihiro, Hokkaido, 080-8555 Japan
Home address:	West 18, South 2, Obihiro, Hokkaido 080-0028 Japan

Education:

1979-1983	School of Veterinary Medicine and Animal Science, Kitasato University Awarded the degree of BSc. in Agriculture
1983-1985	Department of Animal Breeding and Reproduction, Institute of Veterinary Medicine and Animal Science, Kitasato University Awarded the degree of MSc. in Agriculture for a thesis entitled "Studies on the development of mouse embryos derived from fertilization *in vitro*". Work supervised by Professor Yutaka Toyoda
1995	Department of Reproductive and Developmental Biology, Institute of Medical Science, University of Tokyo Awarded the degree of Ph.D in veterinary medicine for a thesis entitled "Studies on the development of zona-free mouse embryos". Work supervised by Professor Yutaka Toyoda

Research and Professional experience:

1985-1997	Researcher at Chugai Pharmaceutical Co., Ltd.
1997-2001	Senior Researcher at Chugai Pharmaceutical Co., Ltd.
2001-present	Professor at Research Unit for Functional Genomics, National Research Center for Protozoan Diseases, Obihiro University of Agriculture and Veterinary Medicine
2002-present	Guest Professor at Department of Developmental and Medical Technology, Graduate School of Medicine, The University of Tokyo
1996-2001	Guest researcher at National Institute of Radiological Sciences, Japan

Membership of academic societies:

Society for the Study of Reproduction (regular member)
Japanese Society of Mammalian Ova Research (councilor)
Japanese Society of Animal Reproduction
Japanese Association for Laboratory Animal Science (councilor)
Japan Atherosclerosis Society
The Molecular Biology Society of Japan
Japanese Cancer Association
The Japanese Society of Veterinary Science
The Japanese Society of Parasitology (councilor)

Editorial Board:

Reproductive Biology and Endocrinology (Paper Reporter)

Awards:

The 1996 Japan Atherosclerosis Society Award for the Distinguished Atherosclerosis Research